Does unilateral basal ganglia activity functionally influence the contralateral side? What we can learn from STN stimulation in patients with Parkinson’s disease

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Brun Y, Karachi C, Fernandez-Vidal S, Jodoin N, Grabli D, Bardinet E, Mallet L, Agid Y, Yelnik J, Welter M-L. Does unilateral basal ganglia activity functionally influence the contralateral side? What we can learn from STN stimulation in patients with Parkinson’s disease. J Neurophysiol 108: 1575–1583, 2012. First published June 27, 2012; doi:10.1152/jn.00254.2012.—In humans, the control of voluntary movement, in which the corticobasal ganglia (BG) circuitry participates, is mainly lateralized. However, several studies have suggested that both the contralateral and ipsilateral BG systems are implicated during unilateral movement. Bilateral improvement of motor signs in patients with Parkinson’s disease (PD) has been reported with unilateral lesion or high-frequency stimulation (HFS) of the internal part of the globus pallidus or the subthalamic nucleus (STN-HFS). To decipher the mechanisms of production of ipsilateral movements induced by the modulation of unilateral BG circuitry activity, we recorded left STN neuronal activity during right STN-HFS in PD patients operated for bilateral deep brain stimulation. Left STN single cells were recorded in the operating room during right STN-HFS while patients experienced, or did not experience, right stimulation-induced dyskinesias. Most of the left-side STN neurons (64%) associated with right dyskinesias were mainly activated (48%), with a predominant increase 4–5 ms after the stimulation pulse and a decrease in oscillatory activity. This suggests that unilateral neuronal STN modulation is associated with changes in the activity of the contralateral STN. The fact that one side of the BG system can influence the functioning of the other could explain the occurrence of bilateral dyskinesias and motor improvement observed in PD patients during unilateral STN-HFS, as a result of a bilateral disruption of the pathological activity in the corticobasal circuitry.

subthalamic nucleus; deep brain stimulation; neuronal activity; dyskinesias; high-frequency stimulation

NEURAL CONTROL OF MOVEMENT is largely lateralized. However, there is evidence to suggest that both the contralateral and ipsilateral basal ganglia (BG) systems are implicated in the execution of a unilateral movement. In animals, the performance of a unilateral movement provokes bilateral single-unit activity changes in the striatum (input of the BG system), the external part of the globus pallidus (GPe), the subthalamic nucleus (STN), and the internal part of the globus pallidus (GPi; the BG output nucleus) (Cheruel et al. 1996; Wannier et al. 2002). Using functional brain imagery in healthy volunteers, the performance of simple unilateral motor tasks has been shown to induce unilateral premotor and primary sensorimotor cortical activation but a bilateral activation of the sensorimotor putamen and GPi (Schozl et al. 2000; Lehericy et al. 2006; Kraft et al. 2007). In parkinsonian [Parkinson’s disease (PD)] patients, unilateral movement-related changes in the STN firing rate and oscillatory activity have been reported bilaterally (Williams et al. 2005; Alegre et al. 2005; Devos et al. 2006). Conversely, unilateral lesion of the GPi or high-frequency stimulation (HFS) of the STN has been shown to induce a bilateral motor improvement in PD patients (Baron et al. 1996; Lang et al. 1997; Alberts et al. 2008; Walker et al. 2009). Unilateral GPi lesions can also lead to a bilateral decrease in levodopa-induced dyskinesias (LID) (Baron et al. 1996; Lang et al. 1997), whereas unilateral STN-HFS can induce bilateral dyskinesias, which has been shown to be predictive of a good postoperative outcome (Houeto et al. 2003). Even though the BG may operate, at least partly, the bilateral control of movement in humans, little is known about how one side of the BG circuitry influences the neuronal activity contralaterally (Lehericy et al. 2006; Kraft et al. 2007) and which BG circuits are involved. In rats, unilateral modulation of STN activity by pharmacological agents or lesion modulates neuronal activity in the contralateral STN (Mouroux et al. 1995; Castle et al. 2005). Two recent studies in PD patients have reported an increase in contralateral STN neuronal activity while stimulating the STN unilaterally (Novak et al. 2009; Walker et al. 2011). In these experiments, however, 1) the recordings were multiunit activity (Novak et al. 2009), 2) the precise location of the recording and stimulation sites were not shown, 3) the motor behavior changes were not...
assessed, and 4) low (30 Hz) and high (160 Hz) stimulation frequencies produced similar effects on contralateral STN neuronal activity, whereas the clinical effects are known to be opposite (Moro et al. 2002). This present study was undertaken to determine the quantitative and qualitative nature of the changes in neuronal activity of the contralateral STN in relation to the changes in motor behavior induced by unilateral STN stimulation. Here, we recorded single-unit left STN activity during right STN stimulation in the presence or absence of right-side dyskinesias.

**MATERIALS AND METHODS**

*Patients.* Seven PD patients (6 women and 1 man, mean age: 59 ± 7 yr) were operated for bilateral implantation of stimulating electrodes into the STN. PD patients included in this study had an advanced form of PD (Hoehn and Yahr “off” score ≥ 3, disease duration: 12 ± 4 yr) (Hoehn and Yahr 1967), a good response to levodopa treatment before surgery [mean improvement in the motor PD disability (unified PD rating scale-UPDRS) part III: 70 ± 20%] (Fahn et al. 1987), with disabling levodopa-induced motor complications (UPDRS part IV: 10.4 ± 6.9) despite optimal medical treatment (mean equivalent levodopa dosage: 700 ± 161 mg/day), absence of dementia [mean minimental status: 27.4 ± 3.1 (Cockrell and Folstein 1988); Mattis scale: 139.3 ± 4.9 (Mattis 1988)], a normal brain MRI, and absence of contraindications to surgery (Welter et al. 2002). One year after surgery, the mean improvement in the motor PD disability with bilateral subthalamic stimulation was 47 ± 11%, with 53% and 72% mean reductions in the anti-PD drug treatment and levodopa-induced complications (UPDRS part IV), respectively. The protocol was supported by Institut National de la Santé et de la Recherche Médicale (RBMC06-02) and approved by the local ethics committee. All patients gave informed written consent.

*Neurosurgical procedure.* The surgery was performed as previously described (Bejjani et al. 2000; Maltete et al. 2007). Drug treatment was discontinued the evening before surgery. Subthalamic nuclei were preoperatively targeted by means of stereotactic MRI (Dormont et al. 2004). The implantation of bilateral stimulating electrodes (model 3389, Medtronic, Minneapolis, MN) was performed the day after using both preoperative anatomic and perioperative electrophysiological targeting and clinical testing.

*Left subthalamic recordings during right-side electrical subthalamic stimulation.* Perioperative electrophysiological recordings were performed in awake but immobile patients at rest. Three to five coaxial leads (a central tungsten recording microelectrode, diameter: 25 μm; impedance: 10 MΩ, and an external tube for macrostimulation, FHC Instruments, Bowdoinham, ME) were lowered stereotactically to 5 mm above the predetermined target along three to five parallel trajectories using a microdrive (Medtronic). Four of the leads were arranged, at a distance of 2 mm, around a central lead positioned according to the stereotactic coordinates, thus allowing stimulation and recording from the central, anterior, posterior, medial, and lateral parts of the STN. Signals were amplified (×10), filtered (300 Hz–3 kHz), audiomonitored, and digitally recorded using a Leadpoint system (Medtronic).

Extracellular single-unit neuronal activity of the left STN (Hutcheson et al. 1998; Rodriguez-Oroz et al. 2001) was recorded 2 min before, during, and after bipolar stimulation of the right STN (mean recording time: 432 ± 32 s, stimulation parameters: 60 μs, 140 Hz, cathodal square pulses, 2 and 4 V) using an external stimulator (Dual Screen model 3628, Medtronic) connected to the definitive electrode previously implanted (Fig. 1A) (Walker et al. 2011). Left subthalamic recorded neurons were included if they were well isolated, stable, and could be sampled for at least 60 s.

As passive movements may induce changes in STN neuronal activity (Rodriguez-Oroz et al. 2001), we chose to record stimulation-induced dyskinesias to objectively assess the effect of unilateral STN stimulation on the ipsilateral side of the body instead of evaluating the clinical therapeutic effects (i.e., rigidity or akinesia). For this purpose, we used surface electromyographic recordings of both right and left leg muscles. This procedure also enabled us to precisely evaluate the temporal relationship between stimulation-induced dyskinesias and the subthalamic neuronal activity changes.

*Single-unit anatomic localization.* During the electrophysiological procedure, control profile images were regularly obtained from right-left projections, with the short X-ray radiological device of the Leksell stereotactic frame, to check the electrode trajectories and depth. This device consists of X-ray-visible fiducial markers and a digital flat panel screen fixated to the stereotactic frame. Before the surgical procedure begun, the direction of the X-ray unit was adjusted to be perpendicular to the stereotactic frame to allow superimposition of the values of the right and left z- and y-scales. The trajectory of each recording electrode was precisely located with reference to the AC-PC reference frame defined by both the stereotactic frame and AC-PC landmarks in the preoperative MRI. Its localization within the STN was then determined using a digital three-dimensional deformable BG histological atlas (Yelnik et al. 2007), which was adjusted to the individual brain geometry of each patient (Bardin et al. 2009). Electrophysiological analysis of single-unit recordings and their atlas-based localization were performed independently and blindly by different experts (Fig. 1A).

*Offline analysis.* Neuronal recordings were exported offline as text files and analyzed using the Spike2 software suite (version 5, CED,
Cambridge, UK). Spikes were discriminated from noise with no stimulus artifact removal method. The mean firing rate, mean inter-spike interval, and coefficient of variation were calculated for each neuron (Kaneoke and Vitek 1996; Welter et al. 2011). Discharge pattern analysis was performed using two methods. First, a discharge density histogram (Kaneoke and Vitek 1996) was constructed for each cell, and the firing pattern was classified as regular, irregular, or bursting. Second, neuronal activity was sampled for each period, and epochs of elevated discharge rate were analyzed for bursts using a Poisson surprise analysis (Legendy and Salcman 1985) carried out using a Spike2 script (Degos et al. 2005). In this experiment, spike trains with spikes of more than five were considered to be bursts (Steigerwald et al. 2008). The mean burst frequency, duration, number of spikes per burst, intraburst frequency, and interburst interval were calculated for each neuron with burst discharges (Steigerwald et al. 2008). Investigation of neuronal oscillations at the single-neuron level was performed as proposed by Muresan et al. (2008). Briefly, this method consists of five steps: 1) the autocorrelogram histogram (ACH) was computed, 2) the ACH was smoothed using a Gaussian kernel, 3) the central peak was removed, 4) a fast Fourier transform was applied to compute the spectrum of the peakless ACH, and 5) the oscillation score was calculated. The analysis was always made for a chosen frequency band, where the two input variables represent the lower and upper limits of the frequency band of interest (f0: 4–8 Hz, α: 8–12 Hz, βlow: 12–20 Hz, βhigh: 20–35 Hz, and γ: >35 Hz). The oscillation score represents the ratio of the magnitude of the oscillation frequency to the average magnitude of the spectrum (oscillation frequency = the highest magnitude in the band of interest/the average magnitude of the spectrum). The average magnitude of the spectrum was computed by integrating the whole frequency spectrum and taking its average, where Magnitude (f) is the estimated magnitude of frequency f in the fast Fourier transform-computed spectrum. The average spectrum was reduced by removal of the central peak from Table 1.

| Table 1. Effects of 2-V right STN high-frequency (140 Hz) stimulation on the neuronal activity of 35 left STN neurons |

<table>
<thead>
<tr>
<th>Frequency, Hz</th>
<th>Before</th>
<th>With STN Stimulation</th>
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<tr>
<td>Mean, ms</td>
<td>27.5 ± 15.4</td>
<td>29.2 ± 20.0</td>
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<tr>
<td>Median, ms</td>
<td>15.8 ± 8.5</td>
<td>16.3 ± 7.4</td>
</tr>
<tr>
<td>Mode, ms</td>
<td>6.4 ± 4.8</td>
<td>6.3 ± 4.6</td>
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<tr>
<td>SD, ms</td>
<td>34.3 ± 26.5</td>
<td>36.0 ± 33.3</td>
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<tr>
<td>Coefficient of variation</td>
<td>1.17 ± 0.35</td>
<td>1.16 ± 0.26</td>
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<tr>
<th>Burst-type activity</th>
<th>Before</th>
<th>With STN Stimulation</th>
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<tbody>
<tr>
<td>Mean bursting index</td>
<td>5.9 ± 1.7</td>
<td>5.8 ± 1.8</td>
</tr>
<tr>
<td>Burst frequency, Hz</td>
<td>0.83 ± 0.55</td>
<td>0.84 ± 0.57</td>
</tr>
<tr>
<td>Number of spikes per bursts</td>
<td>15.5 ± 5.5</td>
<td>13.8 ± 4.6</td>
</tr>
<tr>
<td>Intraburst frequency, Hz</td>
<td>87.8 ± 32.7</td>
<td>85.0 ± 33.4</td>
</tr>
<tr>
<td>Interburst interval, s</td>
<td>1.29 ± 0.87</td>
<td>1.23 ± 0.76</td>
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</table>

Values are means ± SD. STN, subthalamic nucleus. *P < 0.05 compared with prestimulation values (by Wilcoxon rank tests).
Finally, the estimated oscillation frequency was taken as the frequency of the highest magnitude in the band of interest. The strength of the oscillation was given by the oscillation score. Oscillations were considered to be significant for oscillation scores of $10^2$ and a signal-to-noise ratio of $5$ (Muresan et al. 2008).

Statistical analyses. Results are given as means $\pm$ SD. Modifications of the neuronal activity of the left STN (frequency of discharge, characteristic of the bursts, and peak frequencies of the oscillatory activity) during right STN stimulation were studied using the non-parametric Wilcoxon rank test. To examine the modifications of the pattern of discharge and oscillatory activities in the various frequency bands, Bowker’s test of symmetry was used. Statistical analysis was carried out using the Statview software suite.

Comparisons between neurons associated with the occurrence of leg stimulation-induced dyskinesias versus neurons recorded without were performed using the nonparametric Mann-Whitney test. Statistical significance was accepted at $P < 0.05$. No Bonferroni correction was applied.

### RESULTS

A total of 36 single cells were recorded in the left STN before, during, and after STN-HFS of the right STN: 35 cells with 2-V stimulation current, 19 cells with 2- and 4-V stimulation, and 1 cell with 4-V stimulation (Fig. 1). During the 2-V stimulation of the right STN, 14 neurons were recorded in the left STN while dyskinesias occurred in the right leg, and 21 neurons were recorded in the left STN without stimulation-induced dyskinesias (Fig. 1A).

Changes in neuronal activity of the left STN during right leg dyskinesias induced by right STN stimulation (2 V). When right leg dyskinesias were induced by right STN stimulation, firing rate and bursting activity of the left STN neurons were significantly modified (Fig. 2). This was not the case in the absence of stimulation-induced dyskinesias (Fig. 2). Changes are detailed below. On average, left STN neuronal activity was not significantly modified by right STN-HFS at 2 V (Table 1).

#### Mean discharge rate. When right STN-HFS induced right leg dyskinesias, an inhibition was observed in 64% of left STN neurons recorded, with a significant decrease in their mean firing rate (Table 2 and Fig. 2A). This decrease in left-side neuronal activity occurred 76 ms after the start of the right STN stimulation (Fig. 3A, left) and the poststimulus time histogram (PSTH) showed a permanent inhibition of neuronal activity with no time-locked residual neuronal activity (Fig. 3A, right). Conversely, when no dyskinesias occurred, no significant change in the mean firing rate was observed, but there was an inhibition in 24% of left STN neurons and an activation for 48% (Table 2 and Figs. 2A–3B). When the neuron was activated in the absence of stimulation-induced

<table>
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<tr>
<th>140-Hz Stimulation</th>
<th>Dyskinesias</th>
<th>No Dyskinesias</th>
<th>$P$ Value</th>
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<tbody>
<tr>
<td>2 V</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>14</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Inhibition</td>
<td>9</td>
<td>5</td>
<td>0.03</td>
</tr>
<tr>
<td>Activation</td>
<td>2</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>4 V</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Inhibition</td>
<td>6</td>
<td>8</td>
<td>0.58</td>
</tr>
<tr>
<td>Activation</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>1</td>
<td>0</td>
<td></td>
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</table>

$n = 35$ neurons total for 2-V stimulation and 20 neurons total for 4-V stimulation. $P$ values represent the comparison between neurons recorded during stimulation-induced dyskinesias and neurons recorded in the absence of dyskinesias (by Fisher’s exact test).

Fig. 3. Effects of low (2 V) and high (4 V) intensity right STN-HFS stimulation (140 Hz) on left STN neuronal activity in two individual neurons. The left poststimulation time histograms (PSTHs) represent left STN neuronal activity recorded 400 ms before and after 2-V STN-HFS. The right PSTHs represent neuronal activity during the 7 ms after the stimulus pulse histograms before (open bars) and during (shaded bars: 2 V and solid bars: 4 V) STN-HFS. A: left STN neuron recorded during right DSK with a significant reduction in its neuronal discharge rate at both 2- and 4-V stimulation intensities. Note that the decrease in neuronal activity occurred in the first 100 ms after the stimulation was activated. B: left STN neuron recorded while no DSK occurred with a significant increase in its neuronal discharge rate at both 2- and 4-V stimulation intensities. Note that the increase in neuronal activity was time locked with a 4- to 6-ms response.
dyskinesias, the PSTH was differentially affected with an excitation peaking 4–5 ms after the stimulation pulse (Fig. 3B). In three left STN neurons, a very short latency response (<2 ms) was observed with 2-V right STN stimulation (dyskinesia neurons: n = 2, no-dyskinesia neurons: n = 1).

The mean, median, mode, and SD of the interspike interval and the mean coefficient of variation of the discharge pattern of the 35 left STN neurons recorded during 2-V right STN-HFS were not significantly modified during right STN-HFS (Table 1). No significant differences in these neuronal activity characteristics were found in neurons recorded both with or without stimulation-induced dyskinesias (data not shown).

_Bursting activity_. Preceding right STN stimulation, about half of the left STN neurons exhibited a burst type pattern of activity (Fig. 4A and Table 1). Right STN-HFS (2 V) induced significant changes in the distribution of the discharge pattern, with 10 cells switching their firing pattern (P < 0.02; Fig. 4A). The change in discharge pattern was not significantly different between the two groups of neurons, i.e., those recorded in the presence of dyskinesias versus without dyskinesias (29% of changes in both; data not shown).

When right STN-HFS induced right leg dyskinesias, the mean burst frequency (data not shown), intraburst frequency, and interburst interval of the left STN neurons significantly decreased (P < 0.05; Fig. 2, B and C). Conversely, no significant change was observed for left STN neurons recorded when stimulation failed to induce dyskinesias (Fig. 2, B and C).

_Oscillatory activity_. Before stimulation, about half of the neurons exhibited oscillatory activity, mainly in the β-band frequency (12–35 Hz; Fig. 4B). Right STN-HFS (2 V) induced a significant decrease in the proportion of left STN neurons with oscillations (P < 10^-4; Fig. 4B), with a significant decrease in the β-band frequency (data not shown). This decrease was only significant for left STN neurons recorded in the absence of right leg stimulation-induced dyskinesias (57% before vs. 19% during STN-HFS, P < 0.003; Fig. 5). No significant change in oscillatory activity was found for left STN neurons recorded while right leg stimulation-induced dyskinesias occurred (36% before and during STN-HFS).

_Changes in neuronal activity of the left STN during stimulation of the right STN as a function of stimulation intensity_. Increasing the stimulation current did not significantly modify the mean discharge rate of the 19 neurons recorded in the left STN with either the 2- or 4-V stimulation (49.8 ± 21.4 Hz before vs. 46.3 ± 24.5 Hz with 2-V stimulation vs. 44.6 ± 22.2 Hz with 4-V stimulation, P = 0.52). However, during 4-V right STN stimulation, about half of the left STN neurons were activated while one-third were inhibited (P < 0.001; Table 2). In five neurons recorded with both intensities, a very short latency response (<2 ms) was observed when the stimulation was increased to 4 V (Figs. 3B–6).

An increase in right STN-HFS from 2 to 4 V led to 4 of 19 cells changing their discharge pattern when recorded in both conditions: 2 cells switched from a regular to an irregular pattern, 1 cell switched from a regular to a burst-type pattern, and 1 cells switched from a burst-type to a regular pattern (data not shown). The increase from 2- to 4-V stimulation did not significantly modify the effects of right STN-HFS on left STN burst characteristics (data not shown) and oscillatory activity (47% before vs. 16% during 2-V STN-HFS vs. 20% during 4 V STN-HFS, P = 0.06; data not shown). Increasing stimulation current induced an increase in the occurrence of dyskinesias with 12 of 20 neurons recorded during stimulation-induced dyskinesias (P < 0.05; Table 2). Among the 12 neurons recorded with 4-V induced dyskinesias, 6 neurons were previously recorded during 2-V stimulation in the absence of induced dyskinesias. In these six neurons, no significant changes were observed, although there was a tendency for fewer spikes per burst (17.6 ± 5.4 vs. 14.5 ± 4 spikes/burst, P = 0.15).

**DISCUSSION**

In this study, we showed that ipsilateral dyskinesias induced by unilateral STN-HFS were associated with significant changes in contralateral STN neuronal activity, with a decrease in the firing rate and bursting activity but no significant change in oscillatory activity. We also found that an increase in stimulation current induced a short latency activation of neuronal firing. These results are consistent with the hypothesis that the complex changes provoked by unilateral STN-HFS stimulation involve the BG thalamocortical networks bilaterally.

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Technical considerations. Several lines of evidence suggest that these results are robust. First, the recording microelectrodes were localized within the STN, as attested by the neuronal activity recorded, which was similar to that previously reported in PD patients (Hutchison et al. 1998; Rodriguez-Oroz et al. 2001; Steigerwald et al. 2008). Second, the location of recorded STN single cells and stimulating electrodes were precisely determined using a validated three-dimensional histological deformable BG atlas (Yelnik et al. 2007; Bardinet et al. 2009). Third, it is unlikely that a stimulation artifact could have masked the response of left STN neurons to right STN stimulation: the artifact was short (1 ms), the time-locked excitatory response observed in PD patients was maximal 4–6 ms after the stimulation pulse, and very short latency responses (<2 ms) could be detected (Figs. 3 and 6) (Walker et al. 2011). Although a possible role of stimulation artifacts in the decrease in oscillatory activity observed during STN stimulation cannot be totally excluded, the fact that these changes were not observed for all neuronal activity recordings is not in accordance with this hypothesis. Finally, a possible role of dyskinesias in neuronal activity changes observed during stimulation-induced dyskinesias cannot be completely ruled out; the fact that these changes occurred before the emergence of dyskinesias (<100 ms) argues against this explanation (Fig. 3). In addition, a decrease in neuronal activity was also observed.
in some neurons in the absence of stimulation-induced dyskinesias (Table 2).

**Ipsilateral STN stimulation-induced dyskinesias are related to complex changes of neuronal activity in the contralateral STN.** In STN neurons recorded while contralateral dyskinesias occurred, the main effect was a decrease in the firing rate and bursting activity (Fig. 2), with no significant changes in oscillatory activity. This result is in line with the report of an inhibition in neuronal activity of the STN, Gpi, and substantia nigra pars reticulata (SNr) when LID occur in PD patients and animals rendered PD (Filion and Tremblay 1991; Lozano et al. 2000; Boraud et al. 2001; Stefani et al. 2002; Alonso-Frech et al. 2006). Conversely, this result seems to be in contradiction with the increase in glutamatergic transmission observed in the STN, entopeduncular nucleus (EP) (rat Gpi), and forelimb motor cortex in PD patients and PD rats when STN-HFS induced dyskinesias (Boulet et al. 2006; Quintana et al. 2010), which leads, in theory, to an increase in neuronal activity. However, when increasing the intensity of stimulation from 2 to 4 V, we observed an increase in ipsilateral dyskinesias, with an increase in the number of activated neurons (Table 2). This suggests that the neuronal firing rate in the STN is probably not per se the determinant of the occurrence of dyskinesias but that the pattern and level of oscillatory activity may be of greater importance. The reduction in STN bursting activity observed when STN-HFS induced dyskinesias is in line with this hypothesis (Fig. 2) and has also been reported in Gpi neurons (one of the STN outputs) of PD monkeys during LID (Filion and Tremblay 1991; Boraud et al. 2001). The persistence of oscillatory activity in STN neurons during STN-HFS-induced dyskinesias, with even a tendency to have more oscillatory activity (36% vs. 19%), is also in line with this hypothesis and has been previously reported during LID, with, in some reports, an increase in low (4–10 Hz) and high-frequency band oscillatory activity (Lozano et al. 2000; Stefani et al. 2002; Meissner et al. 2005; Alonso-Frech et al. 2006). Finally, these data suggest that dyskinesias induced by STN-HFS are probably mainly related to the pattern of neuronal activity and oscillatory activity and less to the firing rate (Obeso et al. 2000), with a complex combination of these three parameters (Boraud et al. 2001).

**Unilateral STN-HFS modulates contralateral subthalamic neuronal activity.** In our patients, unilateral STN-HFS provoked inhibitory and excitatory responses of the contralateral STN neurons with changes in bursting and oscillatory activity (in particular a decrease in β-band oscillations; Fig. 5). An increased STN firing rate provoked by contralateral STN-HFS has been recently reported in PD patients (Novak et al. 2009; Walker et al. 2011) and may result from an increased excitatory input and/or a decreased inhibitory input to the STN. Anatomic and functional studies have suggested that the STN receives inhibitory GABAergic inputs from the ipsilateral but also contralateral GPe (Castle et al. 2005) and excitatory glutamatergic inputs from the ipsilateral premotor and motor cortices (Nambu et al. 2002), but also (in rats) from the ipsilateral and contralateral parafascicular nucleus of the thalamus (Pi-Th; Mouroux et al. 1995; Castle et al. 2005). The STN projects excitatory inputs, in turn, to the Pf-Th (internal circuitry between the two Pi-Th and two STN sites) (Castle et al. 2005).

Unilateral STN-HFS has been shown to induce an antidromic ipsilateral GPe activation in animals (Sato et al. 2000; Hashimoto et al. 2003) and also a short latency (2.5 ms) ipsilateral activation of neurons of the deep motor cortex in both PD patients and PD rats (Baker et al. 2002; Li et al. 2007; Gradinaru et al. 2009). These two antidromic activations could have opposite effects on the contralateral STN neuronal activity with J for the former, a decrease in both ipsilateral (Welter et al. 2004; Degos et al. 2005) and contralateral STN firing rate (our results); and 2) for the latter, an increase in both ipsilateral (Gradinaru 2009) and contralateral STN firing rate (Walker et al. 2011), via an activation of the contralateral motor cortex and the corpus callosum. The latency of 5–6 ms of the main excitatory response, as previously reported (Walker et al. 2011) and observed in our patients, is consistent with this hypothesis. This excitatory response could also result from an orthodromic activation of both the ipsilateral and contralateral Pi-Th induced by unilateral STN-HFS (Castle et al. 2005), as previously reported in the ipsilateral output efferent structures, such as the Gpi or SNr, in both PD patients and animals rendered PD (Maurice et al. 2003; McIntyre et al. 2004; Galati et al. 2006; Mallete et al. 2007). The very short excitatory response observed in a few neurons could result from an activation of fibers passing through or near the stimulated STN and connected to the contralateral one (Walker 2011). Finally, it appears that the composite effect of these neuronal firing changes is not clearly established, but the complex time-locked responses (activation-inhibition-activation-inhibition) of the
contralateral STN neurons during unilateral STN-HFS probably result from these different antidromic and orthodromic effects. This complex change could also lead to the decrease in the bursting activity of the contralateral STN during unilateral STN-HFS with a more regular discharge pattern, as also previously reported in the ipsilateral output structures (Maltete et al. 2007).

In the present study, we also found that unilateral STN-HFS reduced oscillatory activity in the contralateral STN, mainly in the β-band frequency. In patients and animal models of PD, an increase in β-band oscillatory activity has been identified as a pathophysiological hallmark of the disease and related to the akinesia induced by dopaminergic denervation (Brown et al. 2001) but also as a predictive factor of symptomatic improvement provoked by STN-HFS (Zaidel et al. 2010). In both normal and PD animals, STN-HFS has been shown to produce a significant decrease in β-band oscillations in the ipsilateral STN (Meissner et al. 2005; Gradinaru et al. 2009) but also in the ipsilateral cortex by activation of intracortical inhibitory neurons (Li et al. 2007; Gradinaru et al. 2009; Deniau et al. 2010). Given the known cortical organization, we would expect that this cortical effect could be transmitted to the contralateral motor cortex with a disruption of the abnormal corticostriatal oscillation on the other side and a reduction in β-oscillations in the contralateral STN.

In conclusion, our results demonstrate that unilateral STN-HFS changes the contralateral STN activity in relation to the occurrence of ipsilateral dyskinesias. The fact that one side of the BG influences the functioning of the contralateral BG system may explain the bilateral dyskinesias and motor improvement observed in some PD patients with unilateral STN-HFS (Houeto et al. 2003; Alberts et al. 2008). This bilateral effect could also play a role in the behavioral improvement induced by unilateral STN-HFS observed in some patients with a supposed corticobasal dysfunction, such as patients with obsessive-compulsive disorders (Mallet et al. 2008). Finally, these motor and behavioral clinical effects provoked by unilateral STN-HFS are probably related to a bilateral disruption of the pathological activity in the corticostriatal circuitry.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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